CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ALDRIN

SB 950-085, Tolerance # 135

4/8/87

## I. DATA GAP STATUS

Chronic rat: No studies submitted[1]

Chronic dog: No studies submitted[1]

Onco rat: Data gap, inadequate studies, possible adverse effect indicated.

Onco mouse: Data gap, inadequate studies, possible adverse effect indicated.[2]

Repro rat: Data gap, inadequate studies, possible adverse effect indicated.[3]

Terato mouse: Data gap, inadequate studies, possible adverse effect indicated.[3]

Terato hamster: Data gap, inadequate studies, possible adverse effect indicated.[3]

Gene mutation: No studies submitted[1]

Chromosome: No studies submitted[1]

DNA damage: No studies submitted[1]

Neurotox: No studies required at this time.

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[1]"No studies" means no reports in sufficient detail to evaluate. Some very brief (usually 1 paragraph) summaries are acknowledged in the 1-liners.

[2]A hamster study (013:38148) has been indicated as possibly upgradeable in J. Remsen review of 2/5/86. EPA considers the available mouse studies, taken together, to adequately fill the data gap for mouse oncogenicity.

[3]CDFA has no complete reports of teratogenicity or reproduction studies, however EPA Dec. 1986 Aldrin "Guidance" document (135:014) indicates that there are "Core Supplementary" grade studies, which must be replaced by acceptable teratogenicity and reproduction studies. Terata in mice and hamsters, and some reproductive effects in mice and rats, are indicated (p. 21

of cited EPA document), however only at comparatively high doses in the case of teratogenicity studies, and in the chronic toxicity range in the case of reproduction studies.

** indicates acceptable study
**Bold face** indicates possible adverse effect
File name SB085ALD.CNA Index prepared by N. L. Hughett

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

EPA has recently published an Aldrin Reregistration Guidance document (Dec., 1986), which cites extensively an unpublished Dynamac Aldrin/Dieldrin risk assessment review (Page et al., 1985), which CDFA has requested from EPA. This reviewer recommends an update of this tox summary when that review becomes available.

The Aldrin Reregistration Guidance document (p. 7) notes that "The registrants of dieldrin declined to sponsor the requisite data. As a result, registrations of all termiticide products containing dieldrin were suspended in 1984." Dieldrin is a primary metabolite and environmental degradation product of aldrin, hence some of the one-liners which follow relate partially or exclusively to dieldrin.

CDFA has no Aldrin EPA one-liners on file.

**CHRONIC**

**RAT**

Only a few 1-paragraph summaries relating to rat chronic studies are available to CDFA. The Aldrin Reregistration Guidance document indicates that EPA is satisfied with the LEL estimate of 0.025 mg/kg/day from a rat chronic study (citing the unpublished Dynamac Aldrin/Dieldrin risk assessment review, which CDFA has requested).

135-013 055269 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Rats" (Treon et. al., J. Agric. Food Chem 3 1955:402); Aldrin or Dieldrin fed at 2.5, 12.5 or 25.0 ppm to 40 rats/sex/group; possible slight increase in liver/body weight ratios and nonspecific changes in hepatic cells at all treated levels; **Unacceptable - Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

135-013 055270 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Rats" (Fitzhugh et. al., Fd. Cosmet. Toxicol. 2 1964: 551); Two-year feeding study, aldrin or dieldrin at 0.5, 2, 10, 50, 100 and 150 ppm in the diet to 12 rats/sex/group; Decreased survival at 50 ppm; "Slight" degree of histological liver cell changes at 0.5 and 2 ppm; Lowest effect level - 0.5 ppm; **Unacceptable- Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

135-013 055271 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Rats" (Walker et. al., Toxicol. Appl. Pharmacol., 15 1969: 345) Two-year feeding study, dieldrin, 40 rats/sex/group at 0.1, 1.0 and 10.0 ppm; Increased irritability and occasional convulsions during handling observed at 10 ppm, Increased liver weight at 1.0 and 10.0 ppm, Histopathological liver lesions at 10 ppm; **Unacceptable - Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

**DOG**

Two 1-paragraph summaries are on file. There is insufficient information to evaluate. The Aldrin Reregistration Guidance document indicates no data gap for non-rodent chronic toxicity.

135-013 055272 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Dogs", (Fitzhugh et. al., Fd. Cosmet. Toxicol., 2 1964: 551) 1-2 mongrel dogs/sex/group were fed aldrin or dieldrin at 0.2, 0.5, 1.0, 2.0, 5.0 and 10.0 mg/kg/day for up to 2 years; histopathological changes in liver, kidney and bone marrow at 1.0 mg/kg (both aldrin and dieldrin) and in 0.5 mg/kg dieldrin-fed dogs; Unacceptable - **Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

135-013 055273 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Dogs", (Walker et. al., Toxicol. Appl. Pharmacol., 15 1969: 345), Dieldrin at 0.005 and 0.05 mg/kg/day for 2 years (approx. 0.1 and 1.0 ppm); Increase in alkaline phosphatase after 18th week in high dose animals, increase in liver weight and liver/body weight ratio in high dose females; Unacceptable - **Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

**MONKEY**

135-013 38153 Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Studies in Monkeys," (Zoecon et. al., paper presented at 6th annual meeting, Society of Toxicology, Atlanta, Georgia 3/67; Wright, et. al., unpublished Tunstall Lab. note 10/23/69; Dieldrin at 0.01, 0.10, 0.50, 1.0 and 5.0 ppm for up to 6 years in the diet to groups of 5 Rhesus monkeys/sex/group; slightly enhanced capacity of liver microsomes to hydroxylate certain

substrates and elevation of liver microsomal cytochrome P-450; Unacceptable - **Very Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

**ONCOGENICITY**

The following quote from the EPA Administrator at the time of suspension of most aldrin and dieldrin uses (presumably in 1974) touches oncogenicity findings in rats and mice (see Aldrin Reregistration Guidance document, p. 16):

> "The evidence is conclusive that Aldrin-Dieldrin is carcinogenic in mice. It h produced statistically significant compound-related benign and malignant tumors in t livers of five different strains of mice. It also significantly increases the incid of lung tumors. This evidence of carcinogenicity is supported by additional, though definitive, evidence that Aldrin-Dieldrin has increased the incidence of tumors in r

**RAT**

EPA is requiring an acceptable rat oncogenicity study, as indicated on p. 56 of the A Reregistration Guidance document. The most meaningful oncogenicity study on hand is proba 007:930348 (below).

**135-007 930348** Gulf South Research Institute ((NCI-CG-TR-21)), 1978. "Bioassays of Aldr Dieldrin for Possible Carcinogenicity". Aldrin, Technical (Shell Chemical Co., greater than pure). Dietary treatment of 0, 30 or 60 ppm Aldrin for 74-80 weeks to Osborne-Mendel rats followed by observation period off dose until term kill at weeks 111-113. No NOEL achieve clinical signs observed at both dosages in both sexes: decreased body weights and increas hyperactivity, convulsions during second year of study. Tumor findings: increased incide

thyroid follicular cell tumors in 30 ppm males and females. Also an increase in adrenal cortical adenomas was observed in 30 ppm females (see pp. 28-31, 67-74). **Unacceptable, no upgradeable** (only 2 dose levels, insufficient number of control animals tested, lack of a no individual data, other deficiencies); CDFA review by J. Remsen 5/3/85).

135-013 055261 Title: "Evaluations, 1977 - Toxicological Studies, Special Studies on Carcinogenicity", (FAO, Rome; see tab marked "Toxicology Studies"), Group of 24 Fisher 344 rats/sex/group were fed 0, 2, 10, or 50 ppm dieldrin in the diet for 104-105 weeks; hyperexcitability, tremors and coma observed in high-dose males beginning week 76 and in h dose females beginning week 80, no significant oncogenicity effect indicated in report; Unacceptable - **very brief summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

135-007 55396 Gulf South Research Institute (Same NCI study as 007:930348 above), 1978 "Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity". Dietary treatment with t weighted average (TWA) dosages of 0, 29 or 65 ppm Dieldrin for 80 or 59 week dosing period respectively, to Osborne-Mendel rats, followed by observation period off dose until term k week 110. No NOEL achieved: clinical signs (hyperexcitability, tremors, etc.) observed a dosages in both sexes. Tumor findings: apparent dose-related increased incidence of thyr follicular cell tumors in females. Also an increase in adrenal cortical adenomas was obs in 29 ppm (TWA) females, however not increased in 65 ppm (TWA) females. None of these fi were considered clear evidence of oncogenicity responses, as definitive statistical signif was not observed. C. Aldous, 4/1/87, Filename = 085RTO1.DIE

**MOUSE**

The most important single reference on mouse oncogenicity is probably the unpublished Dynamac Aldrin/Dieldrin risk assessment review (1985), which is being requested by CDFA. tumors are apparently by far the most important tumor type indicated. Although no individ study meets current EPA Guideline requirements, EPA is satisfied that oncogenic potential

mice has been adequately evaluated. CDFA does not have sufficient data to make such a determination.

**135-007 35675** Title: "Bioassays of Aldrin and Dieldrin For Possible Carcinogenicity,"--M NCI, 1978 (NCI-CG-TR-21); Aldrin technical (Shell Chemical Co., greater than 85% pure), Or dietary administration for 90-93 weeks; 50 mice/sex, B6C3F1 mice; 4 or 8 ppm to males (tim weighted average), 3 or 6 ppm to females (time-weighted average); matched controls of 20 untreated males and 10 untreated females; Pooled controls (92 untreated males and 79 untre females; Increase in hepatocellular carcinoma in males at 4 and 8 ppm, Increase in number early deaths in females at 6 ppm, Increase in hyperactivity in treated groups; **Incomplete** individual data); Unacceptable (only two dose levels, insufficient number of control anima dose levels changed, no NOEL); CDFA review by J. Remsen 5/3/85.

**135-005 930349** Title: "Tumorigenic Potential of Aldrin and Dieldrin for Mice," U.S. Dept 1962 (Toxicology and Applied Pharmocology 4 1962: 187-189); Groups of C3HeB/Fe mice (abou 10/sex/group) were fed control diet, 10 ppm aldrin or 10 ppm dieldrin in the diet for two Statistically significant increase in hepatic cell adenoma; Incomplete (3 page journal art Unacceptable--not upgradable (only one dose level); CDFA review by J. Remsen 5/2/85.

135-013 38141 Dose-Response Characteristics of Dieldrin - Mediated Enhancement of Liver Formation in CF-1 Mice, the German Cancer Research Centre, 6/28/82; (Journal Article - See marked oncogenicity); CF-1 mice fed dieldrin at levels of 0.1, 1, 2.5, 5, 10, 20 ppm up to years to determine median time to tumor formation; data from studies conducted during the 1970's are analyzed for dose and time-to-tumor; presents evidence that dieldrin may be a promoter of liver (as apposed to an initiator); Unacceptable - **Not a guideline SB950 Study** Review by J. Remsen 2.5.86.

**135-013 38156** Title: "Summary of Toxicology of Aldrin and Dieldrin, Chronic Exposure, Carcinogenicity Studies" - Mice (Walker et. al, Fd Cosmet. Toxicol. in press) Mice (Carwor Farm No. 1 strain), Dieldrin at 0.1-10.0 ppm over life-span; dose-related increased incide

liver tumors at all treatment levels; Unacceptable - **very brief summary** (one paragraph). Aldous, 4/3/87, no CDFA review worksheet.

**135-007 55395** Gulf South Research Institute (Same NCI study as 007:35675 above), 1978.) "Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity". Dietary treatment of B6C mice with time-weighted average (TWA) dosages of 0, 2.5, or 5 ppm Dieldrin for 80 weeks, followed by additional observation period of 10-13 weeks prior to sacrifice. No NOEL achie clinical signs (hyperexcitability, tremors, etc.) observed at both dosages in both sexes. findings: dose-related increased incidence of hepatocellular carcinomas in males. C. Aldo 4/1/87, Filename = 085MOO1.DIE

**HAMSTER**

135-013 38148 Title: "A Carcinogenicity Study of the Pesticide Dieldrin in Hamsters" Jo Article: J.R.P. Cabral et al., **Cancer Letters** 6: 241-246 (1979) (see second tab marked 'carcinogenicity'); Syrian golden hamsters, 40/sex/group; Dieldrin (95%) (lot 12-PCD-38) a 60 or 180 ppm for life; no adverse effect indicated; incomplete; **Unacceptable - possibly upgradeable**; CDFA review by J. Remsen 2/5/86.

**REPRODUCTION**

**RAT**

**135-005 055384** (p. 25 of M. R. Zavon report, following Tab Ref. 6, 7, and 11) Title: "The Toxicology and Pharmacology of Aldrin and Dieldrin--Effect on Reproduction," Kettering Lab University of Cincinnati, 6/63; Three Generation reproduction in the rat; Aldrin at 2.5, 1 25 ppm; Increased mortality in suckling rats during lactation, Decrease in numbers of pregnancies at 12.5 ppm (aldrin) or 2.5 ppm (dieldrin); **Very Brief Summary**; Unacceptable; Review by J. Remsen [previous record # was apparently 930349, Doc. #135-005], 5/2/85.

135-013 38158 Title: "Summary of Toxicology of Aldrin and Dieldrin, Reproduction Studie Including Teratology", Hine Lab., Report No. 4, May 1967; Three-generation, rat; dieldrin 0.2, 1.0 and 2.0 ppm; increased mortality in $F_{1a}$ generation, but not in $F_{1b}$, $F_2$ or $F_3$; Unacceptable - **Very Brief Summary** (One paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

**DOG**

**135-005 35679** (Tab "Brief", p. 8) "BRIEF IN SUPPORT OF THE SAFETY OF ALDRIN AND DIELDRIN RESIDUES--Reproduction--Dogs" (834), Study at Kansas State College (12/14/51). Present su from Shell Agric. Chem. Div. review (6/21/63); Aldrin or dieldrin fed in the diet at level to 25 ppm to dogs through one pregnancy and litter; High mortality of pups at 3 ppm or abo during lactation; Similar effect noted in ewes fed up to 25 ppm dieldrin (high mortality o lambs during lactation); Very Brief Summary; Unacceptable. NLH/C. Aldous, 4/1/87, Filenam 085DOR1.ALD

Note: J. R. [Gee's] review of study 005:055384 identified an additional reproduction effect (increased mortality in newborn dogs at 3 ppm). Neither NLH nor CNA could find the reproduction dog effect for aldrin in that record. The finding probably should have been attributed to record 005:35679, above, where the reproductive effect in pups was noted. T Zavon review (Vol. 005, Tab ref. 6, 7, and 11) indicated on p. 6 that "In general, the you the animal, the more susceptible it is to insecticidal poisoning".

**TERATOGENICITY**

**GENERAL**

**135-013 38136** Title: "Toxicological Studies, Special Study on Teratology" (see tab mark 'Toxicology Studies'); Evaluations 1977, FAO publication (Ottolenghi et. al., 1974; Terat 9:11-16;), Literature review of toxicology studies with hamsters, mice and rats given aldr and/or dieldrin; possible teratological effects in hamsters given 30 or 50 mg/kg dieldrin 7, 8, and 9 and mice given 15 or 25 mg/kg no teratologic effect was seen in a study with dieldrin orally at 1.5 and 4 mg/kg to mice days 6-14 of gestation; however, body weights w slightly reduced; **Very Brief Summaries**; Unacceptable, CDFA Review by J. Remsen on 2/5/86.

**RAT**

(No individual reports available)

**RABBIT**

(No individual reports available)

**MUTAGENICITY - MISC.**

135-013 38135 Title: "Toxicological Studies, Special Studies on Mutagenicity" (see tab 'Toxicology Studies') Evaluations 1977, FAO publication, Literature review of Ames test, A test with metabolites, host mediated assays, dominant lethal assay, CHO bone marrow assay, micronucleus and heritable translocation test using dieldrin; no adverse effect noted in s report; **Very Brief Summaries**; Unacceptable; CDFA Review by J. Remsen 2/5/86.

Note: CDFA is requesting a memo from I. Mauer to H. Spencer of EPA OPP Toxicology Br dated 6/25/86. This memo may be the best source currently available on mutagenicity studi

EPA is requiring acceptable studies for all three general areas of mutagenicity (Aldrin Reregistration Guidance document, p. 56).

**GENE MUTATION** (No complete studies submitted)

**CHROMOSOME** (No complete studies submitted)

**DNA DAMAGE**

135-013 055262 (7th page after Tab, "Toxicology Studies") Title: "Evaluations, 1977 - Toxicological Studies, Special Studies on Carcinogenicity", (FAO, Rome; see tab marked "Toxicology Studies", see last paragraph under 'Hamster' heading; Ahmed et. al, Mut. Res. 1977:161-174); Treatment of SV-40 transformed human cells with dieldrin; increased inducti DNA repair (long-type excision repair), increased unscheduled DNA synthesis; Unacceptable- **Brief Summary** (one paragraph). NLH/C. Aldous, 4/3/87, no CDFA review worksheet.

135-013 055262 (Same paragraph as previous 1-liner) Title: "Toxicological studies - Hamster" (last paragrph), DNA - (844) - unscheduled DNA synthesis, Evaluations 1977, FAO publication. (Literature review - see Ahmed, et. al., Mut. Res. 42); Increased unschedule synthesis, Increased induction of DNA repair (long-type excision repair); Unacceptable - **V Brief Summary**. NLH/C. Aldous, 4/3/87, (no CDFA review worksheet).

**NEUROTOXICITY**